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(54) Title: COMPOSITION AND METHOD FOR MEDICATED CHEWING GUM DELIVERY SYSTEM

(57) Abstract

A medicated chewing gum delivery system having a substantially liquid free gum base matrix material and at least one active.

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COMPOSITION AND METHOD FOR MEDICATED CHEWING GUM DELIVERY SYSTEM

This is a continuation-in-part application of U.S. Serial No.09/360,896, filed July 26,1999.

Field of the Invention

The present invention relates to medicated chewing gum delivery systems, as well as to a method for making same. In particular, the invention relates to various chewing gum delivery systems containing one or more active substances.

Background of the Invention

Medicated chewing gums that contain active ingredients are known in the art. Active ingredients include those substances which elicit some type of physiological or pharmacological response in the body. As an example, chewing gums containing vapor action nasal decongestants, analgesics or nicotine have been used to deliver medication to the body as the gum is masticated. Formulations are known which attempt to provide an immediate release or sustained release of the active substance, or both. Many times, the active substance is contained within the gum base material to be released upon chewing. Alternately, the active substance is mixed with an edible confectionery shell or coating which surrounds the entire gum base. There are certain disadvantages associated with these and other formulations, however. Addition to the gum base matrix of the active substance often results in a formulation in which the active is bound too tightly within the matrix itself. This can result in an uneven release, a reduced release profile, or no release at all. Many times the gum base materials are simply incompatible with the active substance, and thus provide ineffective release profiles. Including the active within a candy shell may help to ensure a more thorough release, but the release is immediate and short-lived. The consumer often gets an overwhelming burst of active which is followed by a rapid decrease or dissipation of the effect. Other chewing gum systems utilize granulates made up of gum base material which are compressed together to provide a final formulation. These formulations, however, have not been optimally

utilized to date to provide a truly effective delivery system for active substances.

What is therefore needed in the art are new medicated chewing gum delivery system formulations which provide a more effective and reliable immediate and/or sustained release profile than is presently obtainable in the art.

Summary of the Invention

The invention provides a medicated chewing gum delivery system for active ingredients containing no added moisture which can provide immediate and/or sustained release of one or more active ingredients.

In a further embodiment of the invention, there is provided a chewing gum delivery system having a gum base matrix containing no added moisture which facilitates release of the active substance in either an immediate release or a sustained release profile, or both.

Also provided as part of the invention is a medicated chewing gum delivery system comprising compressed granulates of gum base material having interspersed therebetween one or more active substances for delivery in an immediate and/or sustained release fashion. The gum base matrix may be composed of one or more hydrophilic or hydrophobic materials, depending upon the active substance to be utilized and the release profile desired.

In yet another embodiment, a chewing gum delivery system has a gum base matrix containing essentially no moisture which at least partially surrounds a centerfill containing one or more active substances.

Another embodiment of the present invention includes a medicated gum delivery system in which a coating material at least partially surrounds a gum base matrix. The coating material can contain one or more active substances for immediate and/or sustained release.

It is within the scope of the invention that any of the foregoing embodiments be utilized separately or together, as hereinafter set forth.

Further provided as part of the invention is a method of forming the chewing gum delivery systems described herein.

Detailed Description of the Preferred Embodiments

The invention provides a medicated chewing gum delivery system for one or more active ingredients. The active ingredient may be dispersed into or onto a

gum base matrix comprising ingredients which are essentially moisture, or water, free to facilitate its release according to an immediate or a sustained release profile. In certain preferred embodiments, the chewing gum delivery system will provide for both immediate and sustained release of the active and will be essentially moisture, or water free.

In one embodiment, there is provided a chewing gum delivery system comprised of a gum base matrix which facilitates release of the active. The gum base matrix will include at least one gum base material which may be selected from the many water- and saliva-insoluble gum base materials known in the art. Illustrative examples of suitable polymers for gum bases include both natural and synthetic elastomers and rubbers, as well as mixtures thereof. Naturally-derived polymers include, for example, substances of plant origin like chicle, jelutong, gutta percha and crown gum. Synthetic elastomers such as butadiene-styrene copolymers, isobutylene and isoprene copolymers (*e.g.,* "butyl rubber" in the art), polyethylene, polyisobutylene, polyvinylesters such as polyvinylacetate, and mixtures of any of the foregoing may be particularly useful.

In one embodiment, it is highly preferable that the gum base be selected so as to provide a final chewing gum composition which has a relatively "soft" chew both at the onset of mastication, as well as towards the end of the chewing process (about 20 to 30 minutes or so). Another desirable characteristic of the gum base should be its ability to facilitate the release of the active ingredient(s), hereinafter described, as well as the subsequent absorption thereof by the mucosal membranes. Thus, one or more gum base materials that are at least partially hydrophilic in nature are especially desirable. It is even more preferred that the material have significant hydrophilic characteristics. Of these types of material, polyvinylacetate is particularly preferred. Especially preferred is low to medium weight polyvinylacetate. Polyvinylacetate having a molecular weight (MW) of about 12,000 to 45,000 is even more desirable. In an especially desirable embodiment of the invention, the amount of polyvinylacetate (PVA) in the gum base is maximized with no butyl rubber present, and the quantity of non-

PVA polymers such as butadiene-styrene, butylene-based polymers and copolymers is preferably minimized. It has now been discovered that inclusion of polyvinylacetate provides a gum base which often yields a softer, less brittle and less sticky chewing gum composition, thereby contributing to a more organoleptically pleasing chewing sensation. Polyvinylacetate also tends to be more hydrophilic in nature, and may allow for better release of the saliva-soluble ingredients from the gum composition, referred to in more detail below.

In another preferred embodiment of the invention, the type of gum base utilized includes at least some butyl rubber (copolymer of isoprene and isobutylene), with additional amounts of polyisobutylene, and with polyvinylacetate (preferably PVA having a MW of approximately 12,000) also being present. This butyl-rubber based material appears to have certain advantages when used together with certain types of actives, such as for example nicotine in the form of a salt.

The gum base matrix (in whatever embodiment) will typically comprise from about 40 to 90% of the total chewing gum composition of the invention (unless otherwise stated, all percentages provided herein are weight percentages, based on either the total weight of the gum base matrix or of the final chewing gum composition, where noted). It is more preferred to utilize less than about 70% by weight of chewing gum base matrix material. In certain embodiments too much gum base may interfere with the release of the active material, and additionally, may contribute to tackiness and poor mouth-feel of the final product. In an especially preferred embodiment of the invention, the chewing gum composition will contain about 50 to 60% of gum base matrix, and desirably about 55%. Of the foregoing amounts, about 25 - 75% thereof, more preferably about 30 - 60% thereof, will be the gum base polymer material(s) heretofore described.

An especially preferred gum base matrix formulation will therefore include polyvinylacetate having a molecular weight of about 12,000 (about 14% of the total chewing gum composition), polyisobutylene (about 5% of total), and butyl rubber (about 4% of total). Together these polymers will comprise about 35 - 45%

by weight of the gum base matrix, most preferably about 40%.

The gum base matrix may additionally contain other ingredients well known in the art and selected from the group consisting of plasticizers and softeners to help reduce the viscosity of the gum base to a desirable consistency and to improve the overall texture and bite. These compounds are also noted for their emulsifying properties. As non-limiting examples, compounds such as lecithin, mono- and diglycerides, lanolin, stearic acid, sodium stearate, potassium stearate, glycerol triacetate, glycerol monostearate and glycerin are provided. Stearic acid, lecithin and mono- and diglycerides are particularly preferred. Plasticizers and softeners are desirable as part of the formulation because in addition to softening the primary gum base polymeric compound, they also seem to facilitate release of the active upon mastication. When added, the plasticizers and softeners will comprise from about 0.1 to 20% of the gum base matrix formulation, and more desirably will be within the range of about 5 - 15% thereof.

Waxes such as beeswax and microcrystalline wax, and fats/oils such as soybean and cottonseed oils are also contemplated as part of the gum base formulation. These compounds also function as softening agents. Typically, these compounds (either alone or in combination) will comprise from zero up to about 25% of the gum base matrix, more preferably will make up less than about 20% by weight of the gum base matrix, and even more desirably will constitute about 15 - 20% of the gum base matrix. An especially desirable formulation will include a combination of microcrystalline wax and partially hydrogenated soybean oil in an approximate 1:2 weight ratio. A more exhaustive listing of these compounds, along with recommended weight percentages, may be found in any available industry reference.

Other materials which may be included as part of the gum base matrix include elastomer solvents. These are typically selected from the group consisting of rosin and resin material typically utilized in the confectionery chewing gum industry. Examples include methyl, glycerol, and pentaerythritol esters of rosins or modified rosins, such as hydrogenated, dimerized or polymerized rosins or

mixtures thereof. More specific examples include pentaerythritol ester of partially hydrogenated wood rosin, pentaerythritol ester of wood rosin, glycerol ester of wood rosin, glycerol ester of partially dimerized rosin, glycerol ester of polymerized rosin, glycerol ester of tall oil rosin, glycerol ester of wood rosin and partially hydrogenated wood rosin and partially hydrogenated methyl ester of rosin, such as polymers of alpha-pinene or beta-pinene, and terpene resins including polyterpene and mixtures thereof. Elastomer solvents can comprise from about zero to 75% of the gum base. It is preferable, however, to minimize or even eliminate the quantity of rosin/resin in the gum base. It is especially desirable not to exceed about 10% by weight of the gum base matrix with rosin/resin compound(s).

Filler material may also be present in the gum base matrix as part of the composition of the invention. This material is further selected to enhance the chewability of the final chewing gum composition. In at least some embodiments, certain filler material may also enhance the release and absorption of certain actives, such as for example nicotine and other tobacco alkaloids. Those fillers which are substantially non-reactive with other components of the final formulation are also preferred. Desirable filler materials will therefore include calcium carbonate, magnesium silicate (talc), as well as dicalcium phosphate, and any mixtures thereof. Particularly preferred may be dicalcium phosphate. Other metallic mineral salts may also be utilized as filler material, as for example alumina, aluminum hydroxide, and aluminum silicates, provided they possess the characteristics heretofore set forth. Filler material will typically comprise about 0.1 to 30% of the gum base matrix, and more preferably will be within the range of about 10 to 20% thereof.

Trace amounts of standard industry preservatives such as butylated hydroxy toluene (BHT) may also be present in amounts less than about 0.1% or so of the gum base. Colorants and dyes may also be utilized, if desired.

Further provided as part of the medicated chewing gum composition of the invention are one or more sweeteners. These are included to impart a palatable

sweetness or savoriness to the final formulation. Sweeteners can be chosen from the known saccharide material available in the industry. Sweeteners can include mono-, di- and tri- and polysaccharide materials, either alone or in combination, and their related oligomers. Invert sugar, sucrose, fructose, maltose, dextrose, polydextrose, polydextrin, glucose (corn syrup), maltodextrin (corn syrup solids) etc. are just some examples of suitable sweeteners. Other highly suitable sweeteners include saccharin, aspartame, acesulfame, sucralose, and sugar alcohols such as sorbitol, mannitol, maltitol, isomalt, xylitol as well as other commercially available sweeteners such as the dihydrochalcone compounds, glycyrrhizin, glycerine, Stevia Rebaudiana (Stevioside), and the hydrogenated starch hydrolysates. Of the foregoing, those sweeteners considered in the industry to be "sugarless" or "non-sucrose" are perhaps more preferred. Particularly preferred in some formulations are those sweeteners known to be non-cariogenic or anti-cavity, such as xylitol, sorbitol, maltitol, isomalt, lactitol and polydextrose, either alone or in combination. Other sweeteners contemplated by the skilled artisan which are typically utilized in the food or confectionery industry may also be used. The sweeteners are added in amounts equal to about 0 - 40% of the composition, and preferably within the range of about 0.01 - 20%. More preferably, the sweeteners will comprise about 0.1 - 10% of the final medicated chewing gum formulation according to its various embodiments.

Flavor oils traditionally utilized in chewing gum preparations are also a component of the medicated chewing gum of the invention. These may be selected from a wide variety of natural and synthetic oils and essences known in the industry. Peppermint oil, spearmint oil, cinnamon oil, oil of wintergreen, menthol, menthone, citrus oils and other fruit oils and essences are the most commonly used flavor oils which are employed in the present invention. Additional flavorings may be chosen from extracts of plant material, as well as aldehyde and ester flavorings, both natural and man-made. These flavors will typically comprise from about 0.1 to 10% of the chewing gum composition.

Regardless of the ingredients used, the present active delivery system

gum formulas contain no added water, or ingredients containing water. Moisture is detrimental to the storage stability of a gum delivery system. The absence of moisture in the present invention overcomes a long standing need for storage stabile medicated gums.

Flash-flow processing of one or more of the various edible, water-soluble components heretofore described (non-gum base polymer) as comprising the chewing gum composition is contemplated. Thus, for example, the flavor oil(s) and saccharide materials may be processed together in a flash-flow apparatus for intimate mixing and dispersion upon addition to the gum base material. "Flash-flow" processing involves subjecting a feedstock to conditions of temperature and force which induce the feedstock to rapidly undergo physical and/or chemical transformation. The time during which the feedstock material is subjected to temperatures is extremely short. The term "flash-flow" has become recognized as referring to the conditions of temperature and force required to transform a solid feedstock having a certain morphological and/or chemical structure into a different morphological and/or chemical form without subjecting the materials to the excess heat or other requirements inherent in other forms of processing. Flash-flow processing can be accomplished either by either the flash heat method or via a flash shear method.

In the flash heat process, a spinning machine developed by Fuisz Technologies Ltd. of Chantilly, VA and patented under U.S. Patent Nos. 5,427,811, 5,458,823 and 5,834,033 may be preferred. This patent describes a spinning machine which has a series of elongated heating elements arranged in between a base and a cover. The heating elements, base and cover together define a chamber into which a non-solubilized feedstock material is inserted which is capable of intraparticle flow upon application of heat and force. Means are provided for individually heating each of the elongated heating elements, and restriction means in the form of a cylindrical shell or annular plate which circumscribes the heating elements permits restrictive flow of the processed feedstock which is expelled from the chamber. Other apparatus and methods

useful in the flash-heat process include those set forth in U.S. Patent No.s 5,445,769, 5,447,423 and 5,458,823. The apparatus is operated at the temperature and speed which permits flash heat of the feedstock without deterioration of any of its ingredients, and these parameters can easily be optimized by those skilled in the art. In flash-flow processing, the time during which the feedstock material is subjected to elevated temperature is very short. In the flash-heat method, the feedstock is subjected to elevated temperature usually for only tenths of a second, and in the flash-shear method the feedstock is subjected to elevated temperatures for a time on the order of seconds. This has specific benefits in situations when materials might be degraded or otherwise detrimentally affected by excessive exposure to heat.

In the flash shear process, a shearform matrix is formed by thermally controlling the feedstock material, which includes a non-solubilized carrier, to a point where the carrier undergoes intra-particle flow. The carrier component is preferably a saccharide-based material. The feedstock is advanced and ejected from the machinery while the carrier is undergoing intra-particle flow and is then subjected to disruptive fluid shear forces to form multiple parts or masses, also known as microparticulate dispersions. The feedstock may be delivered to the ejector via one or more extruding devices or other mixing apparatus known in the art such as high and low shear mixers, as for example, Littleford type mixers. The flash shear process also contemplates the use of vertical and horizontal type mixers to deliver the feedstock to the actual flash shear apparatus.

An apparatus for flash shear processing of the feedstock is described in U. S. Patent 5,380,473. The means for shearing is arranged proximally to the ejector and is disposed to effect the shear of the feedstock while it is in the internal flow condition. Preferably, the means for shearing is the means for delivering fluid such as air at sufficient velocity against the feedstock stream as it exists a nozzle. Such a device can be an external atomizing nozzle. The stream of air is directed against the feedstock exterior by the nozzle to provide discontinuities in the feedstock and basically transform the morphology of the

original feedstock into a new morphology achieved by free-flow solidification as discontinuous masses. In Figure 3 of the '473 patent, an air stream is in fluid communication with an annular channel which surrounds the internal nozzle device. Feedstock is fed to the nozzle and is subjected to high velocity air which is created by the combination of tortuous path exits provided by an air cap and a retaining ring. In another embodiment, the means for shearing can also be a chamber in which the environment can be maintained to induce shear upon the collision of a high velocity of a stream of feedstock directed against a preselected and maintained environment.

The individual components of the novel composition herein described may thus be subjected to flash shear processing as well. Those skilled in the art may find that flash-shear methodology and parameters can be further adjusted to their particular needs. Whether processed by flash-heat or flash-shear methods, the flash-flow processed material is combined with the chewing gum base materials to provide intimate mixing and dispersion within the gum base matrix.

Further included as part of the novel medicated chewing gum composition are one or more active substances, either alone or in combination with one another. Active substances include any materials, which when ingested produce some type of effect within the body, whether physiological, pharmacological, biological, or chemical etc. Actives can include solid, semi-solid and liquid substances, but are more desirably solid or semi-solid. A listing of suitable actives may be found in U.S. Patent No. 5,582,855, and these include antitussives (*e.g.*, dextromethorphan, dextromethorphan hydrobromide, noscapine, carbetapentane citrate and chlorphedianol hydrochloride), antihistamines (*e.g.*, chlorpheniramine maleate, phenindamine tartrate, phyrilamine maleate, doxylamine succinate, phenyltoloxamine citrate), decongestants (*e.g.*, phenylephrine hydrochloride, phenylpropanolamine hydrochloride, pseudoephedrine, hydrochloride ephedrine), alkaloids (*e.g.*, codeine phosphate, codeine sulfate and morphine), mineral and nutraceutical supplements (*e.g.*, potassium chloride and calcium carbonate, other calcium salts, magnesium oxide, and other alkali and alkaline metal salts),

nutaceuticals in the form of herbals (ginkoba, St. Johns wort, ginseng, etc.) laxatives, vitamins, e.g. vitamin D3, antacids, ion exchange resins (*e.g.*, nicotine ion exchange resins), anti-cholesterolemics, anti-lipid agents, antiarrhythmics, antipyretics, analgesics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, anti-infectives, psycho-tropics, antimanics, stimulants, gastrointestinal agents, sedatives, antidiarrheal preparations, anti-anginal drugs, vasodialators, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, antitumor drugs, anticoagulants, antithrombotic drugs, hypnotics, anti-emetics, anti-nauseants, anti-convulsants, neuromuscular drugs, hyper- and hypoglycemic agents, thyroid and antithyroid preparation, diuretics, antispasmodics, uterine relaxants, mineral and nutritional additives, antiobesity drugs, anabolic drugs, erythropoietic drugs, antiasthmatics, cough suppressants, mucolytics, anti-uricemic drugs, and mixtures thereof.

Especially preferred actives include pharmaceutical substances, and of these, over-the-counter preparations are desirable. For example, cough and cold actives, especially those with "vapor action" characteristics may be useful. Menthol, for example, is contemplated. Other antitussive and antihistamine actives are also useful. Certain chemical stimulants may also be utilized. Among these, caffeine is desirable, as is nicotine, *e.g.* nicotine polacrilix or nicotine salts such as nicotine hydrogen tartrate. Other active substances may include analgesics as well, as for example aspirin and non-aspirin pain relievers like acetaminophen and ibuprofen. Nutraceuticals are also desirable. Actives will typically comprise from about 0.01 to 50% of the chewing gum delivery system of the invention.

One or more of the active substances and/or flavorants or sweeteners may be provided as part of an encapsulation matrix. In this way, the active is preserved and enrobed within the chewing gum until it is consumed by the customer. Encapsulations may be prepared using methods known in the art. In

order to effectively encapsulate the active ingredients, one or more other food-grade materials are employed as processing aids. These food grade materials can include oleaginous material, as well as saccharides, proteins and other non-toxic polymeric material, especially those materials with emulsifying properties. Highly suitable encapsulation processing aids are preferably oleaginous material, *e.g.* fats and oils. It is believed that the oleaginous material surrounds and enrobes individual particles of the active ingredients, thereby creating a matrix of several thousand or even more individually enrobed particles once combined into the final chewing gum composition. Suitable oleaginous material includes various food-grade oils and fats available in the industry. Of these, those with emulsifying properties are often particularly desirable. Vegetable and animal oils and fats may be utilized for this purpose. Stearine may be utilized as an encapsulating agent, while certain mono- and diglyceride-based fat products are also efficacious. Canola oil, soybean oil and cottonseed oils may be preferred as well in certain embodiments. Also useful are one or more while medium chain triglyceride (MCT) oils, as well as other mono-, di- and triglyceride based fatty acid oils. Oleaginous material as encapsulating/processing aids will typically comprise about 0.1 to 40% of the chewing gum composition of the invention, and more desirably will make up from about 0.1 to 15% thereof. The skilled artisan may utilize more or less of the foregoing amounts, depending upon such factors as the type and quantity of active substance(s) to be utilized, the particular oleaginous material(s), the degree of encapsulation desired, as well as the overall mouthfeel contemplated in the final medicated chewing gum composition. In addition to the active ingredient(s), it is also within the scope of the invention that one or more of the heretofore described flavorants may also be encapsulated according to the methods herein described.

Various encapsulation techniques may be utilized to provide the encapsulated active substance matrix as part of the chewing gum composition of the invention. In one embodiment, the flash-shear processing techniques set forth in U.S. Patent No. 5,380,473 can be utilized. The techniques of the 473 patent

may be further utilized in conjunction with a unique tower device in which material to be encapsulated is provided in free fall by a sprayer at the top of the tower, and an encapsulant material such as oleaginous substances is extruded in the form of droplets to coat and encapsulate the dry, particulate material exiting the tower. This is described, for example, in Irish Patent Application No. 980395. Other methods available in the art such as, *e.g.* spray-drying, atomizing and simple and complex extrusion processes are also within the scope herein set forth. Simple mixing methods with industrial scale mixing equipment (Hobart and Sigma type mixers) may also be utilized to prepare encapsulations, either alone or in combination with any of the foregoing other encapsulation methods as well.

In addition to the foregoing components, the medicated chewing gum delivery system according to at least one embodiment may optionally contain a buffer material or system. Buffering agents are those compounds which adjust the pH inside the mouth and thereby assist the mucous membranes in the absorption of the active substance once it is released from the formulation upon chewing. In certain instances, it may be preferable to utilize those compounds which help to create a basic or alkaline pH environment inside the mouth and saliva, either alone or in combination with one another. Of these, certain salts such as for example, sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate, potassium citrate and dipostassium phosphate, including one or more mixtures thereof, are particularly preferred. Potassium carbonate may often be especially desirable, as well as admixtures of potassium carbonate and potassium bicarbonate. Other known buffering agents or buffering systems known in the art may also be utilized. The buffering agent will comprise about 0.1 to 10% of the delivery system chewing gum formulation, and when used in conjunction with an active such as nicotine, may desirably be within the range of about 0.5 to 5% thereof. In particular, an about 1 to 5% quantity of buffer may be especially desirable in the final formulation. In one preferred embodiment of the invention, it is preferable that the buffer system be adapted so as to yield a pH in excess of at least about 7.5 inside the mouth, and even more desirably in excess

of about 8.0, or even greater than about 8.5. As heretofore stated, the presence of the buffering system not only seems to facilitate absorption of certain actives such as nicotine inside the mouth, but also seems to facilitate the release of nicotine from certain nicotine ion exchange resins, in particular nicotine polacrilix, as well as from nicotine salts. At the same time, the buffer system is preferably optimized so that it does not result in a "dumping" of nicotine inside the mouth which would overwhelm the user. The quantity and type of buffer materials furthermore should not cause unpleasant organoleptic side effects, such as irritation, burning, coughing or choking, etc. The buffer system to be utilized in this embodiment of the invention can provide a predictable, yet sustained and manageable release of actives such as nicotine, as well as aid in the absorption thereof by the mucosal membranes.

In still a further embodiment of the invention, there is provided one or more of non-cariogenic, anti-cavity and tooth whitening ingredients to be incorporated into one or more of the medicated chewing gum delivery systems herein described. These are preferably utilized with the non-cariogenic sweeteners heretofore described. U.S. Patent No. 5,762,911 describes anti-cariogenic agents such as calcium salts, arginine and a cariostatic anion such as a organic phosphate compound. Tooth-whitening compounds include, for example, kaolin, calcium carbonate, silicon dioxide and certain cellulosic materials.

The foregoing ingredients making up the chewing gum delivery system, e.g. gum base matrix, sweetener(s), active(s) optional buffers and filler(s) etc., of the invention may be admixed together to produce the final formulation using mixing methods known in the art. For example, the gum base may be heated and softened using the heretofore described solvent material, and then blended with sweeteners, flavors and actives, etc. The result is a medicated chewing gum delivery system in which the active is reliably released both upon initial mastication and upon sustained chewing thereafter. An internal delivery system is thereby achieved, in which the active substance is an "internal" or integral part of

the gum base. Since the gum base matrix is desirably chosen to facilitate release of the active substance, then the amount of actual mastication may be preferably be minimized. In other words, the end user may in many instances simply "park" the composition inside the mouth and still attain reliable release. The invention according to at least one embodiment thereby achieves a goal of an excellent immediate release and/or sustained release profile.

In a particularly preferred embodiment, the active material(s) together with the non-actives, heretofore described, are provided in a substantially non-liquid format. That is, the formulation of the invention is substantially 0% liquid. Typically, chewing gum formulations comprise three major components. These are gum base, solids and liquids. By excluding substantially all liquid from the formulation, incompatibility problems between the various components are avoided, as are the concomitant problems of instability (especially of the active materials), migration and interaction among the actives, flavors, sweeteners and buffers, etc.

In a further embodiment of the invention, there is provided a chewing gum delivery system in which a gum base matrix material in the form of granulates has one or more active substances interspersed among the granulates. The gum base granulates together with the active(s) are compressed to yield the final formulation. The gum base matrix may be material as heretofore described, i.e. that which facilitates release of the active (as for example that having a hydrophilic moiety), or may be other gum matrix material known in the art. For example, a low moisture, non-aqueous gum base matrix having a high degree of hydrophobicity may be utilized in certain formulations. In certain situations, the gum base matrix material and the active(s) can have different, somewhat incompatible moieties so that the active is not strongly retained by the gum base matrix, and can be released more easily.

In this embodiment of the invention wherein gum base granulates are used, it is especially desirable that the active substance(s) be thoroughly dispersed among the gum base granulate matrix, but preferably not be contained

within the granulates themselves. It may also be desirable that the active substance substantially enrobe or surround each of the individual granulates as well.

To therefore prepare this embodiment of the medicated chewing gum composition of the invention, the procedures set forth in U.S. Patent No. 4,405,647 may be especially helpful to the skilled artisan. Briefly stated, the gum base material may be melted or softened using one or more of the softening agents, plasticizers and/or solvent and filler materials heretofore described. The sweeteners and flavors, whether processed via flash-flow processing or other traditional mixing methods, are then admixed into the gum base. This is accomplished by comminuting the gum base material together with the water-soluble ingredients in a bed or blender within a gaseous medium at room temperature, as described in the 647 reference. This material is continuously pulverized and thereby chopped into much smaller particles. To prevent adherence of the resultant particles to one another, additional filler or bulking material may be added like lubricants, glidants and other tableting and compression aids well known in the pharmaceutical industry, such as for example, silica gel or calcium carbonate. Granules of any desired size and shape may be obtained upon the introduction of a standard mess screen to separate the particulates once formed.

The next step in forming the final chewing gum composition involves adding the active substance to the formed particulates. This is done by admixing the actives, whether encapsulated or in free form, with the pulverized materials so as to substantially disperse the particulates. In a preferred mode, the active is added along with the tableting, lubrication or other compression aids. The active material thus becomes substantially entrapped in the multitude of spaces between the individual gum particles. Upon thorough mixing by any suitable device, the materials are then compressed and compacted in a tablet press or other suitable device. In this way the active materials are sandwiched in the voids in between the compressed particulate gum granulate material. The active substance is

thoroughly dispersed between and throughout the resulting matrix. The active is thus "external" to the gum base material itself. The result is an external delivery system for the active material. In a particularly preferred embodiment, the active material(s) together with the non-actives, heretofore described, are provided in a substantially non-liquid format. That is, the formulation of the invention is substantially 0% liquid.

The composition of the invention thus achieves intimate mixing and dispersion of one or more active ingredients without embedding the actives within the gum base material itself. In a preferred embodiment, one or more actives are interspersed between particulates of the gum base. Subsequent release of the active thereby becomes less dependent on the mastication effort of the consumer. The active ingredient has merely to be released from between the gum base material, rather than from within the actual granulates. This embodiment may therefore be particularly desirable in an immediate-release chewing gum delivery system. In addition, the formulation of the invention can easily be adapted to a sustained release formulation as well by inclusion of many particulates (with actives therebetween or coated thereon) within the final composition. The more particulates there are, the more spaces between which active may be interspersed.

A preferred example of the foregoing embodiment provides for an active substance such as nicotine to be encapsulated in an oleaginous matrix which is then utilized to coat and/or surround the gum base particulates. In this way, the nicotine can be subsequently released upon chewing, and is not bound up by the gum matrix itself. Any of the gum base materials heretofore described may be utilized to make up the granulate matrix, which can then be utilized with the nicotine.

In still a further embodiment of the invention, there is set forth a medicated chewing gum delivery system having a gum base matrix which at least partially surrounds a centerfill fluid. The centerfill will contain one or more active substances. The centerfill may be a liquid or semi-liquid material and preferably is

low fat or is fat free. In addition to the active(s), the centerfill may contain one or more sweeteners and/or flavorants as heretofore described. A combination of saccharide material, flavoring, polyol and edible gel material is one example. One or more of the active ingredient(s) and/or the sweeteners and flavorants, etc. may be encapsulated as previously set forth, and then incorporated into the centerfill.

The centerfill embodiments may be prepared using methods known in the confectionery and chewing gum industries. For example, U.S. Patent No. 3,806,620 describes a method for forming centerfill chewing gum by extruding a hollow-centered rope of chewing gum through an orifice having a pair of concentric conduits extending therethrough. A centerfill material is fed through the inner conduit to the hollow center upstream through a space between the inner and outer conduits. The centerfill rope of chewing gum is passed to a sizing unit having a plurality of pairs of rollers for progressively decreasing a cross-sectional dimension of the gum rope. The plurality of pairs of rollers includes at least one vertical pair of rollers having vertically aligned axes or rotation and overlapping lower flange portions. Ramp means are provided for guiding the gum rope above the roller flange portions upon entry of the gum rope between the vertical pair of rollers. Other methods of forming centerfill chewing gum known in the art may also be utilized.

The centerfill embodiment may be particularly desirable wherein immediate release of the active is desired. Encapsulating the active ingredient(s) in this embodiment may help to taste-mask those actives which provide an undesirable organoleptic sensation. Other than the centerfill, it is preferred that the formulation ingredients of this embodiment also be substantially liquid-free, or about 0% liquid.

Any of the foregoing medicated chewing gum delivery systems herein described may be further formulated with a coating material to yield yet another embodiment of the invention. The coating material will at least partially surround the entire chewing gum composition according to the latter's various embodiments. The coating material may be a water-soluble confectionery shell

which dissolves upon contact with saliva. Alternatively, the coating material may be a water-insoluble material, such as a polymeric gum base material which is the same or different from the gum base matrix itself. The coating material can contain one or more active substances, or be substantially devoid of actives. In addition, the coating material and the gum base matrix may contain the same or different active substances. In this way, the skilled artisan can have an immediate release of one active from the coating material, followed by a more sustained release of the same or another active from the gum base matrix.

EXAMPLES

Examples of the delivery system were prepared in gum form and tested for effectiveness and performance of nicotine delivery. Two different gum bases served as ingredients for the examples. GUM BASE X included butyl rubber in an amount by weight of about 5.0%, polyisobutylene in an amount by weight of about 9.0%, rosins in an amount by weight of about 10%, polyvinyl acetate in an amount by weight of about 24%, plasticizer in an amount by weight of about 20%, emulsifier in an amount by weight of about 6.5%, microcrystalline wax in an amount by weight of about 5.0%, and dicalcium phosphate in an amount by weight of about 20.5%. GUM BASE Y, by contrast, included mono & diglycerides E471 in a form commercialized under the trademark MYVAPLEX 600 and in an amount by weight of about 40%, mono & diglycerides in a form commercialized under the trademark DUREM 117 and in an amount by weight of about 40%, soy lecithin in a form commercialized under the trademark CENTROL 3F UB and in an amount be weight of about 19.9%, and dicalcium phosphate anhydrous FCC in an amount by weight corresponding to about 0.1%.

The nicotine in some of the following examples can be provided in encapsulated form. An exemplary encapsulation form, referred to hereinafter as "ENCAPSULATION FORM I" includes nicotine hydrogen tartrate USP in an amount by weight of about 13.51%, MANNITOL 35 in an amount by weight of about 28.83%, and Sorbitol (NEOSORB P 60 W) in an amount by weight of about 57.66%. Another exemplary encapsulation form, referred to hereinafter as

"ENCAPSULATION FORM II" includes nicotine hydrogen tartrate USP in an amount by weight of about 12.98%, Sorbitol in an amount by weight of about 43.02%, Mannitol 35 in an amount by weight of about 29%, and MYVAPLEX 600P (mono & diglyceride, 90%) in an amount by weight of about 15%. Yet another exemplary encapsulation form, referred to hereinafter as "ENCAPSULATION FORM III" includes nicotine hydrogen tartrate salt USP in an amount by weight of about 14.57% and Sorbitol in an amount by weight of about 85.43%.

In the following examples, the nicotine delivery system of the invention was compared to certain control formulations, as well as the commercial formulation available under the trademark Nicorette®. Comparisons were made in the ability of the delivery systems to release nicotine and also control the pH of saliva in the mouth, thereby resulting in effective absorption of nicotine into the bloodstream. Release of nicotine from the delivery system was measured by analysis of the remaining nicotine in the delivery system at timed intervals following human subjects chewing gum samples. The pH of saliva was measured during chewing by collection of saliva samples. For each "chew out" study, the following protocol was observed: A serving size of gum (approximately 1.0 gram each) was chewed at a timed rate of 15 chews per minute by human subjects for different chewing intervals up to a total period of 30 minutes. Each serving of gum contained approximately 2 mg. of nicotine. At the intervals noted on the graphs corresponding to the Examples, the amount of residual nicotine remaining in the gum was measured to determine the percentage released within that time period. Nicotine measurements were made by High Performance Liquid Chromatography (HPLC). Calibration curves were constructed with standard nicotine solutions. The amount of nicotine released was determined by subtraction of the residual amount of nicotine from the starting amount. Saliva pH measurements were made utilizing a calibrated pH meter. In addition, blood specimens were collected from subjects during chewing and nicotine concentrations were measured by gas chromatography-mass spectrometry (GC-MS). Deuterated nicotine was used as the internal standard and standard nicotine calibration solutions were processed

along with the specimens. The limit of quantitation of the GC-MS assay was 1-ng/mL.

Example 1

In this example, chew out studies were conducted with five human subjects using Formula A according to one embodiment of the invention, and 2 mg NICORETTE gum. Formula A contained nicotine hydrogen tartrate (approximately 2.2 mg of nicotine base). In addition, the delivery system of Formula A was buffered with 45 mg of potassium carbonate. More specifically, Formula A included GUM BASE X in an amount by weight of about 55%, GUM BASE Y in an amount by weight of about 4.5%, nicotine in ENCAPSULATION FORM I in an amount by weight of about 5%, Sorbitol (NEOSROB P 60 W) in an amount by weight of about 28%, potassium carbonate USP (extra fine) in an amount by weight of about 4.5%, mint flavor in an amount by weight of about 2.4%, and AF menthol in an amount by weight of about 0.6%. In addition, talc USP (e.g,. MP98-30) was added as a processing aid in an amount by weight substantially equal to the amount of menthol.

The NICORETTE formulation released its nicotine quite slowly over the entire 30 minute period. Formula A, on the other hand, provided a rapid release of nicotine within the first 3 - 10 minutes, followed by continued slower release thereafter, resulting in overall greater release of nicotine compared to 2 mg Nicorette.

The release rate (mg nicotine released/minute) over time for Formula A was compared to 2 mg Nicorette. The early rapid release of nicotine by Formula A was three times faster over the first 3 minutes of chewing compared to 2 mg Nicorette. Following a very fast initial rate of 0.12 mg/minute over the first 3 minutes, Formula A released at an average rate of 0.07 mg/minute over the remaining period of mastication. In the case of 2 mg Nicorette, the release rate was nearly constant throughout the entire mastication period ranging from 0.03 mg/minute to 0.06 mg/minute. The maximum rate of nicotine released by Formula A (0.12 mg/minute) was two-fold greater than the maximum release rate of

Nicorette (0.06 mg/minute).

Example 2

In this example, chew out studies were conducted with five human subjects using Formula B according to another embodiment of the invention and compared to 2 mg NICORETTE gum. Formula B contained nicotine polacrilex (approximately 2 mg of nicotine base). More specifically, Formula B included GUM BASE X in an amount by weight of about 55%, sorbitol NEOSORB P 60W in an amount by weight of about 22.27%, xylitol CM 90 in an amount by weight of about 16%, a flavoring substance in an amount by weight of about 2.5%, nicotine polacrilex in an amount by weight of about 1.23%, potassium carbonate in an amount by weight of about 2%, and potassium bicarbonate in an amount by weight of about 1%.

Each serving of the delivery system of Formula B was buffered with a combination of 20 mg of potassium carbonate and 10 mg of potassium bicarbonate. The NICORETTE formulation released its nicotine quite slowly over the entire 30 minute period. Formula B, on the other hand, provided a rapid release of nicotine within the first 3 - 10 minutes, followed by continued slower release thereafter, resulting in slightly greater release of nicotine compared to 2 mg Nicorette. Formula B was also more effective in early release of nicotine over the first 10 minutes of chewing compared to 2 mg Nicorette. Thus, this formulation containing the same nicotine moiety (nicotine polacrilex) and content as 2 mg Nicorette released substantially more nicotine at a faster rate over the entire chewing period as a result of the improved properties of the gum base.

Example 3

In this example, the pH of saliva during chewing was measured during the chew out period (20 chews/minute) for five formulations, namely, Formula C, Formula D, Formula E, Formula F, and Formula G. Formula C included GUM BASE X in an amount by weight of about 55%, Sorbitol (NEOSORB P 60 W) in an amount by weight of about 17%, Xylitol milled USP VCC in an amount by weight of about 16%, a buffering system of potassium carbonate USP (extra fine) in an

amount by weight of about 4.5%, nicotine in hydrophilic ENCAPSULATION FORM III in an amount by weight of about 5%, and cooling mint flavor in an amount by weight of about 2.5%.

Formulas C, D, E, and F were identical, except that the buffering systems consisted of the following: Formula C, 45 mg of potassium carbonate (4.5% by weight); Formula D, 30 mg of potassium carbonate (3.0% by weight) and 15 mg of potassium bicarbonate (1.5% by weight); Formula E, 15 mg of potassium carbonate (1.5% by weight) and 30 mg of potassium bicarbonate (3.0% by weight); and Formula F, 45 mg of potassium bicarbonate (4.5% by weight).

Formula G was unbuffered and included GUM BASE X in an amount by weight of about 55%, Sorbitol in an amount by weight of about 25.31%, Xylitol in an amount by weight of about 16%, mint flavor in an amount by weight of about 3%, and nicotine hydrogen tartrate in an amount by weight of about 0.69%.

The pH of saliva during chewing was progressively increased with increasing proportions of potassium carbonate. This demonstrates that a buffering system as part of a nicotine delivery system greatly facilitates a higher pH environment inside the mouth. Such a buffering system can be adjusted to deliver a desirable amount of buffer. This, in turn, further facilitates the absorption of a pH dependent compound such as nicotine.

Example 4

For this example, salivary pHs (mean data for 5 subjects) during chewing of Formulas A and G (unbuffered) were compared with salivary pHs of 2 mg NICORETTE gum chewed at the same rate (15 chews/minute) by the same subjects.

During chewing of Formula A, the pH of saliva increased within the first 1 minute to a maximum pH of 9.05 and was followed by a decline to approximately 8.30 at 5 minutes and an even slower decline to normal levels over the remaining 20 minutes. In contrast, the pH of saliva during chewing of 2 mg Nicorette increased slowly to a maximum of approximately 7.88 at 5 minutes followed by a very slow decline over the remaining time. Formula G illustrates the small

changes in pH that occur naturally by the stimulating action of chewing upon salivary contents. This demonstrates that the buffering system of Formula A is releasing buffer rapidly in the early stages of chewing at the appropriate time to greatly facilitate the absorption of nicotine.

Example 5

This example illustrates mean plasma data from four subjects who chewed Formula A and 2 mg Nicorette. During chewing, blood specimens were collected, centrifuged and plasma separated for analysis by GC-MS. Starting baseline levels (zero time) were subtracted from measured nicotine concentrations at each time of collection. Release of nicotine from Formula A gum resulted in a rapid increase in blood levels over the first 10 minutes of chewing compared to 2 mg Nicorette gum. Nicotine levels continued to increase over the 30 minute chewing period for both gums. The early rapid release of nicotine by the Formula A gum resulted in a nicotine blood level difference of approximately 3 ng/mL at 10 minutes. Continued release of nicotine by the Formula A gum ultimately produced a difference of approximately 4 ng/mL at 30 minutes. This demonstrated the effectiveness of the Formula A gum in providing early and sustained release of nicotine into the oral cavity followed by effective absorption into the bloodstream across the oral mucosa as a result of buffer control of saliva pH conditions.

Example 6

For this example, the effect of softening agents was observed on the nicotine release rate. Formulas C, H, and A included the exemplary GUM BASE X, which is butyl-rubber-based, together with nicotine hydrogen tartrate as the active. The buffering system was provided in the form of 45 mg. of K_2CO_3 per serving. Formula H included GUM BASE X in an amount by weight of about 55%, GUM BASE Y in an amount by weight of about 2.3%, Sorbitol (NEOSORB P 60 W) in an amount by weight of about 30.2%, mint flavor in an amount by weight of about 2.4%, a buffering system consisting of potassium carbonate USP (extra fine) in an amount by weight of about 4.5%, AF menthol in an amount by weight of

about 0.6%, and nicotine in ENCAPSULATION FORM II in an amount by weight of about 5.0%. Formula H also included some talc USP MP98-30 as a processing aid in an amount by weight equal to the menthol.

Formulas A and H included softening plasticizers (e.g., MYVAPLEX 600, DUREM 117, and the like) according to preferred embodiments of the invention. Formulation C did not contain any such softening plasticizers. Loading of softening plasticizer was 1/3 higher in Formulation A than in H. Formulations A and H both facilitated a higher nicotine release rate within about 10 minutes than did Formulation C.

The foregoing examples demonstrate how changes in the formulation of the gum base and/or changes in the buffering system can be used to modify how the nicotine (or actives that behave like nicotine) is delivered. While the foregoing examples include the butyl-rubber-based GUM BASE X, it is understood that the invention is not limited to the exemplary embodiments. Non-butyl-rubber-based gums, for example, can be used to implement alternative embodiments of the present invention.

Example 7

In this example, a chew out study was conducted using Formula J, and compared to Nicorette gum. Formula J contained 60% gum base matrix, of which approximately 35-40% was PVA polymer material (with no butyl rubber), along with 100% nicotine polacrilex as the nicotine active. The delivery system of Formula J was buffered using a combination of sodium carbonate and sodium bicarbonate in about a 2:1 weight ratio. Each serving of the delivery system included 20 mg. of the sodium carbonate and 10 mg of the sodium bicarbonate. The same participant chewed each gum separately over time at a rate of 10 chews/minute. The Nicorette formulation released its nicotine quite slowly over the entire 30 minute period. Formula J, on the other hand, provided an excellent release of nicotine within the first 3-5 minutes, and a steady release thereafter.

Example 8

For this example, another chew-out study was conducted using a different participant. Formula J was again utilized, as was Nicorette gum. Formula K also was tested. Formula K was identical to Formula J, except that 100% nicotine salt (nicotine tartrate) served as the nicotine active. The chew rate was 20 chews/minute over the course of 30 minutes total. Again, Formula J of the invention had an excellent release rate of nicotine. The release rate of Formula K was not quite as fast as that of Formula J.

Example 9

In this example, the pH generated as a result of chewing was measured during the chew out period (20 chews/minute) for three formulations, namely, Formula J, Nicorette, and Formula L. Formula L was identical to Formula J, except that it contained 55% gum base matrix and the buffering system was a combination of potassium carbonate and potassium bicarbonate. The pH obtained with Formulas J and L were considerably higher than was the pH obtained with the Nicorette formulation. This demonstrated that a buffering system as part of a nicotine delivery system greatly facilitates a higher pH environment inside the mouth. This, in turn, further facilitates the absorption of a pH-dependent compound such as nicotine. Notably, the rise in pH occurred early in the chewing process.

The invention also provides that the buffering system heretofore described may be utilized with any type of confectionery formulation in which a controlled release under proper pH, and preferably alkaline pH conditions, is warranted. However, the absence of water in the gum formulas has been shown to provide a highly effective delivery system.

The foregoing exemplary embodiments provide a convenient, reliable, practical, and relatively painless system for delivering an active. They are capable of delivering initial and second doses of a craving reduction active or other actives (a bi-phasic delivery), the combination of which rapidly reduces cravings, or provides some other pharmacological effect, and provides the pharmacological effect or protection from such cravings over a prolonged period of time beyond the

initial dose. Notably, the delivery system of the present invention is capable of rapidly achieving a pharmacologically effective concentration of the active (e.g., nicotine) in the bloodstream (e.g., within 5 minutes, or more desirably within 3 minutes, or in some cases, within 1-2 minutes), and is also capable of keeping the concentration of the active in the bloodstream at or near the pharmacologically effective concentration for at least 20 minutes after chewing of the delivery system begins, or more desirably about 30 minutes to about 50 minutes after chewing begins.

While the foregoing examples contain only one form of the active (e.g., nicotine hydrogen tartrate or nicotine polacrilex) for both the initial and second doses of the active, it is understood that the active can be provided in more than one form. The initial dosage, for example, can be delivered using one form of the active, and the second dosage can be provided by another form of the active.

Similarly, the exemplary dosage amount of about 2 milligrams is not a limitation of the present invention. It will be appreciated from the foregoing teachings that alternative dosage amounts can be provided (e.g., 1-10 milligrams of nicotine, or more desirably, 1-4 milligrams) by suitably modifying the composition that defines the delivery system, especially if the active is not nicotine.

The invention also provides that the buffering system heretofore described may be modified to compliment any active delivery system in which proper pH is necessary or warranted to improve adsorption of that active by the host.

It is expected that certain changes or modifications to the invention herein described may be effected by those skilled in the art without departing from the true spirit and scope thereof as set forth in the claims and the accompanying specification.

CLAIMS:

What is claimed is:

1. A medicated chewing gum delivery system comprising one or more active substances, and a gum base matrix which facilitates release of said active substance according to at least one profile selected from the group consisting of immediate release and sustained release, said chewing gum delivery system being substantially moisture free.

2. The medicated chewing gum delivery system of Claim 1, wherein said gum base matrix comprises a polymer which is substantially hydrophilic, said polymer being selected from the group consisting of low to medium molecular weight polyvinylacetate.

3. The medicated chewing gum delivery system of Claim 2, said gum base matrix having substantially no butyl rubber.

4. The medicated chewing gum delivery system of Claim 1, wherein said polymer comprises butyl rubber, polyisobutylene and polyvinylacetate having a molecular weight of about 12,000.

5. A medicated chewing gum delivery system comprising compressed granulates of gum base material having interspersed therebetween one or more active substances, said delivery system providing at least one profile selected from the group consisting of immediate release and sustained release wherein said chewing gum is substantially moisture free.

6. The medicated chewing gum delivery system of Claim 5, wherein said gum base material is selected from the group consisting of non-aqueous polymers

having hydrophobic moieties.

7. The medicated chewing gum delivery system of Claim 6, further comprising a coating material which surrounds said delivery system.

8. A medicated chewing gum delivery system comprising a substantially moisture free gum base matrix, wherein said gum base matrix enrobes or surrounds a centerfill comprising one or more active substances in liquid or semi-liquid medium.

9. The medicated chewing gum delivery system of Claim 8, wherein said active substance is encapsulated in an oleaginous material.

10. A method of forming a medicated chewing gum composition delivery system which comprises the steps of:

a) forming gum base granulates;

b) dispersing at least one active substance between said granulates; and

c) compressing said granulates and said active substance into a chewing gum composition, wherein said chewing gum is substantially moisture free.

11. The method according to Claim 10, wherein said step a) further comprises admixing at least one gum base material with at least one member selected from the group consisting of sweeteners and flavorants.

12. The method according to Claim 11, wherein said gum base material is at one least one polymer having at least partial hydrophobic moieties.

13. The method according to Claim 12, wherein said active substance is provided as part of an encapsulation.

14. The method according to Claim 13, wherein said active substance is encapsulated using a flash-shear process.

15. The method according to Claim 14, wherein said active substance is at least one member selected from the group consisting of antitussives, antihistamines, analgesics, and chemical stimulants.

16. The medicated chewing gum composition of Claim 15, wherein said active substance is at least one stimulant selected from the group consisting of caffeine derivatives.

INTERNATIONAL SEARCH REPORT

Interr .nal Application No
PCT/US 99/23018

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/00 A61K31/465 A61K31/52

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 January 2000	04/02/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Stoltner, A

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INTERNATIONAL SEARCH REPORT

Intern ıal Application No
PCT/US 99/23018

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Information on patent family members

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